Amendments to the Specification

The following amendments are made to correct typographical errors in the specification. The paragraph numbers used refer to the numbering in the application as published (U.S. Patent Application Publication No. 2004/0242490).

Please add the following header and paragraph to the application in the position following paragraph [0001] and preceding the header "FIELD OF THE INVENTION:"

STATEMENT OF FEDERALLY-SPONSORED RESEARCH

The present invention was made with Government support under a contract 2RO1CA91645 awarded by the National Institutes of Health. The United States Government may have certain rights to this invention pursuant to the grant.

Please replace paragraph [0010] with the following amended paragraph:

[0010] Inhibition of angiogenesis would be a useful therapy for restricting tumor growth and metastases. Inhibition of angiogenesis may be effected by (1) inhibition of release of "angiogenic molecules" such as, for example, bFGF (basic fibroblast growth factor), (2) neutralization of angiogenic molecules, (e.g., anti-bFGF antibodies), and (3) inhibition of endothelial cell response to angiogenic stimuli. (Folkman et al., Cancer Biology, 3:89-96 (1992)). Several potential endothelial cell response inhibitors have been described that might be used to inhibit angiogenesis, e.g., collagenase inhibitors, basement membrane turnover inhibitors, angiostatic steroids, fungal-derived angiogenesis inhibitors, platelet factor 4, thrombospondin, arthritis drugs such as D-penicillamine and gold thiomalate, vitamin D3 analogs, and alpha-interferon. Additional proposed inhibitors of angiogenesis have also been described in the literature. (Blood, et al. (1990); Moses et al. (1990) Science 248:1408-1410; Ingber, et al. (1988) Lab. Invest., 59:44-5 1; and U.S. Pat. Nos. 5,092,885; 5,112,946; 5,192,744; and 5,202,352.)

Please replace paragraph [0026] with the following amended paragraph:

[0026] FIG. 2 is a chart which illustrates B16 murine melanoma cell adhesion to untreated denatured collagen type-IV (NT), CLK-peptide treated denatured ~~collage~~ collagen type-IV, and SHR-peptide treated denatured collagen type-IV.

Please replace paragraph [0033] with the following amended paragraph:

[0033] As used herein, the term "angiogenesis" includes a variety of processes involving neovascularization of a tissue including "sprouting", vasculogenesis, or vessel enlargement, all. ~~All~~ of which angiogenesis processes involve disruption of extracellular matrix collagen in blood vessels. Angiogenesis that takes place during traumatic wound healing, corpus leuteum formation and embryogenesis is a part of normal physiology. The majority of angiogenesis cases, however, are associated with disease processes.

Please replace paragraph [0036] with the following amended paragraph:

[0036] As used herein "native collagen" refers to collagen that is ~~predominately~~ predominantly in its triple helical form.

Please replace paragraph [0044] with the following amended paragraph:

[0044] As defined herein, a "patient" is any mammal in which treatment of angiogenic diseases, tumor growth or metastasis is desirable. Preferred patients include agricultural or domestic mammals; for example, a pig, a cow, a horse, a goat, a sheep, a mule, a donkey, a dog, a cat, a rabbit, a mouse, ~~and~~ or a rat. An especially preferred patient is a human.

Please replace paragraph [0060] with the following amended paragraph:

[0060] Peptide antagonists of the invention also can be generated using molecular evolution techniques as disclosed in Zhao, H., et al. (2002) Cur. Opin. Biotechnol., Vol. 13:104-110 and Guo, Z., et al. (2002) Biochemistry, Vol. 41:10603-10607. Libraries of proteins can be generated by

mutagenesis, gene shuffling or other well known techniques for generating molecular diversity. Protein pools representing numerous variants can be selected for their ability to bind to denatured collagen, for instance, by passing such protein pools over a solid matrix to which a denatured collagen has been attached. Elution with gradients of salt, for example, can provide purification of variants with affinity for the denatured collagen. A negative selection step also can be included whereby such pools are passed over a solid matrix to which native collagens have been attached. The filtrate will contain those variants ~~with in~~ within the pool that have a reduced affinity for the native form of the collagen.

Please replace paragraph [0061] with the following amended paragraph:

[0061] The peptide and polypeptide antagonists of the present invention also can be generated by phage display. Phage display is a selection technique in which a peptide is expressed as a fusion with a coat protein of a bacteriophage. The result is that the fused protein is displayed on the surface of the ~~viron~~ virion and the DNA encoding the fusion protein resides within the ~~viron~~ virion. (Smith G. P. (1985) Filamentous fusion phage: Novel expression vectors that display cloned antigens on the ~~viron~~ virion surface. Science. 228:1315-1317; Smith G. P., et al. (1993) Libraries of peptides and proteins displayed on filamentous phage. Methods Enzymol. 217:228-257) Phage display allows for rapid identification of peptide ligands for a variety of target molecules using an in vitro process called panning. Panning is carried out, for example, by incubating a library of phage-displayed peptides with a microtiter plate coated with the target, washing away the unbound phage, and eluting the bound phage. The eluted phage is then amplified and taken through additional binding/amplification cycles to enrich the pool in favor of binding sequences. After 3-4 rounds of panning, individual clones are identified by DNA sequencing.

Please replace paragraph [0064] with the following amended paragraph:

[0064] A peptide or polypeptide can be identified as an antagonist through the use of a solid phase ELISA to determine whether the peptide or polypeptide binds to denatured or native collagens. The ELISA assay is useful with a variety of collagen types; for example, the ELISA assay can be used with ~~collagens~~ collagen types, I, II, III, IV and V, as well as for other extracellular matrix

components. The level of binding affinity can be determined by surface plasmon resonance technique (analyzed on a ~~BIOCORE~~ BIACORE 2000 system) (Liljeblad, et al. (2000) Glyco. J., vol. 17:323-329) and standard measurements by traditional scatchard binding assays (Heeley, R. P. (2002) Endocr. Res., Vol. 28:217-229).

Please replace paragraph [0070] with the following amended paragraph:

[0070] KGGCLK-peptide is one such modified peptide. ~~,~~ KGGCLK-peptide is CLK-peptide with sequence KGG added to the N-terminus and GKA added to the C-terminus. The coupling of the amino acids may be accomplished by techniques familiar to those in the art and provided, for example, in Stewart and Young, 1984, Solid Phase Synthesis, Second Edition, Pierce Chemical Co., Rockford, Ill.

Please replace paragraph [0071] with the following amended paragraph:

[0071] The antagonist can be conjugated with cytotoxins such as cisplatin, vinblastine and gemcitabine, for delivery to a tumor or other tissue undergoing angiogenesis, tumor growth, metastasis, arthritis or other disease or condition associated with cellular interactions with denatured collagen type-IV. Such conjugates can be made with a cytolysin or an exotoxin, for example ricin A, diphtheria toxin A, or Pseudomonas exotoxin and fragments thereof. The cytotoxic agent can also be ~~a~~ radioactively labeled with an isotope so as to locally deliver a toxic dose of radioactivity to an angiogenic tissue, tumor growth, metastasis or other tissue undergoing cellular interaction with denatured collagen type-IV.

Please replace paragraph [0105] with the following amended paragraph:

[0105] Potency of a denatured collagen type-IV selective antagonist can be measured by a variety of means including, for example, inhibition of angiogenesis in the CAM assay, in the in vivo rabbit eye assay, or in the in vivo chimeric mouse:human assay as discussed herein.

Please replace paragraph [0116] with the following amended paragraph:

[0116] The therapeutic composition of the present invention can include pharmaceutically acceptable salts of the components therein. Pharmaceutically acceptable salts include the acid addition salts (formed with the free amino groups of the polypeptide) that are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, tartaric, mandelic and the like. Salts formed with the free carboxyl groups also can be derived from inorganic bases such as, for example, sodium, potassium, 3 ammonium, calcium or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine and the like. Particularly preferred are the salts of TFA and ~~HCl~~ HCl.

Please replace paragraph [0126] with the following amended paragraph:

[0126] Subtractive phage display was used to generate peptides that specifically bind to denatured collagen type-IV. Peptide were expressed as a fusion with a coat protein of a bacteriophage on the surface of a ~~viron~~ virion. Panning was carried out by incubating a library of phage-displayed peptides with a microtiter plate coated with the target (native collagen type-IV in wells 1-4, denatured collagen type-IV in well 5), washing away the unbound phage, and eluting the specifically-bound phage. The eluted phage was taken through repeated panning to enrich the pool in favor of binding sequences.

Please replace paragraph [0135] with the following amended paragraph:

[0135] The coating solution of the fifth well was poured off and the well was filled with blocking buffer (0.1M $NaHCO_3$ (pH 8.6), 5 mg/ml BSA, 0.02% ~~NaN3~~ NaN_3, filter sterilized and stored at 4° C.). Next, the fifth well was incubated for 60 minutes at 4° C. The blocking buffer solution was then discarded and the fifth well was washed six times with TBST. Supernatant from the fourth well was then pipetted onto the fifth well and the fifth well was incubated for 60 minutes at room temperature. Next, the solution was poured off the fifth well and the fifth well was washed ten times with TBST.

Please replace paragraph [0139] with the following amended paragraph:

[0139] Human denatured collagen type-IV (25 μg/ml) was immobilized on 48-well nontissue culture treated plates. Wells were washed and incubated with 1% BSA (bovine serum albumin) in PBS (phosphate-buffered saline) for one hour at 37° C. Subconfluent HUVECs (human umbilical vein endothelial cells) were harvested, washed, and resuspended in adhesion buffer containing RPMI-1640 medium, 1 mM $MgCl_2$, 0.2 mM $MnCl_2$, and 0.5% BSA. HUVECs (10^5) were resuspended in 200 μl of the adhesion buffer in the presence or absence of each of the synthetic peptides and were added to each well and allowed to attach for 30 minutes at 37°C. The unattached cells were removed and the attached cells were stained for 10 minutes with crystal violet as described by Petitclerc, et al. (1999) Integrin ~~$\alpha g\beta 3$~~ $\alpha v\beta 3$ promotes M21 melanoma growth in human skin by regulating tumor cell survival. Cancer Res. 59:2724-2730. The wells were washed three times with PBS and cell-associated crystal violet was eluted by addition of 100 μl of 10% acetic acid. Cell adhesion was quantified by measuring the optical density of eluted crystal violet at a wavelength of 600 nm.